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Disturbed development of the enteric nervous system after *in utero* exposure of selective serotonin re-uptake inhibitors and tricyclic antidepressants. Part 2: Testing the hypotheses

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Antidepressant use has increased in the last decade. Several studies have suggested a possible association between maternal antidepressant use and teratogenic effects. In a review of the pharmacologic literature we showed that antidepressant exposure might disturb the development of the enteric nervous system.

WHAT THIS STUDY ADDS

- *In utero* exposure to selective serotonin re-uptake inhibitors (SSRIs) in the second and third trimester or to tricyclic antidepressants (TCAs) in the first trimester leads to a significant increase in laxative use compared with non-exposed children. SSRI exposure was not associated with significant increased antidiarrhoeal medication use, but TCA exposure was.

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AIMS

Antidepressant use has increased in the last decade. Several studies have suggested a possible association between maternal antidepressant use and teratogenic effects.

METHODS

The pharmacy prescription database IADB.nl was used for a cohort study in which laxative and antidiarrhoeal medication use in children after *in utero* exposure to antidepressants (TCA, SSRI, fluoxetine or paroxetine exposed) was compared with no antidepressant exposure. Laxatives and antidiarrhoeal medication use were applied as a proxy for constipation and diarrhoea respectively, which may be associated with disturbed enteric nervous system (ENS) development.

RESULTS

Children exposed *in utero* to SSRIs (mainly fluoxetine and paroxetine) in the second and third trimester or to TCAs in the first trimester, more often received laxatives. Combined exposure to TCAs and SSRIs in pregnancy was associated with a 10-fold increase in laxative use. *In utero* exposure to SSRIs is not associated with antidiarrhoeal medication use compared with non-exposed children. In contrast, antidiarrhoeal medication use was significantly higher in children exposed to TCAs anytime in pregnancy.

CONCLUSIONS

The increased laxative use after second and third trimester exposure to SSRIs might be explained through the inhibitory effect of the serotonin re-uptake transporter (SERT) and because of selectivity for the 5-HT_{2B} receptor which affects the ENS. TCA exposure during the first trimester leads to increased laxative use probably through inhibition of the norepinephrine transporter (NET). Exposure of TCAs anytime in pregnancy leads to increase diarrhoeal use possibly through down-regulation of α_2 -adrenoceptors or up-regulation of the pore forming α_{1c} subunit.

Introduction

Antidepressant use has increased during the last decade [1, 2]. Women are advised to step down pharmacotherapy before conception and to switch to, for example, psychotherapy [3–10]. The use of selective serotonin re-uptake inhibitors (SSRIs) especially during pregnancy seems not to be evidence based [11].

Several studies have suggested a possible association between maternal antidepressant use and teratogenic effects, but these studies are frequently complicated by methodological issues. Studies about the teratogenic risk of maternal tricyclic antidepressant (TCA) use present contradictory results. A Swedish study found an increased risk of heart defects after maternal clomipramine use [12], while other studies have found no teratogenic effects after TCA use during pregnancy or before conception [13–16].

Several cohort studies that examined the use of SSRIs in pregnancy found no increased risk of major congenital anomalies [17–21], while other cohort studies have reported an association between SSRI use and adverse pregnancy outcomes such as low birth weight, short gestational age and an increased prevalence of minor congenital anomalies [18, 22]. Paroxetine is associated with an increased risk for cardiac anomalies and pulmonary hypertension. Therefore paroxetine is contra-indicated just prior to conception and during pregnancy [23–31]. In addition, an association between maternal use of fluoxetine and infantile hypertrophic pyloric stenosis (IHPS) was reported [32]. However many studies have reported no teratogenic effects for TCAs, SSRIs or any other antidepressant [19–21, 26, 33–37], although the statistical power of published studies is low [38].

There were no case reports or studies found reporting disturbed bowel function when exposed to antidepressants *in utero*. The previously conducted pharmacological literature study [39] showed that SSRIs could influence the development of the enteric nervous system (ENS) in two ways: (i) through inhibition of the serotonin re-uptake transporter (SERT) and (ii) through binding of some SSRIs (fluoxetine and paroxetine) to the 5-HT_{2B} receptor. Since the SERT plays a role in the development of the ENS by regulating the 5-HT concentrations, blockage of these transporters during fetal development could influence migration, differentiation and survival of cells. This could lead to abnormal development in the first trimester of pregnancy. The 5-HT_{2B} receptor mediates the growth factor-like action of 5-HT on developing enteric neurons. It is possible that stimulation of 5-HT_{2B} receptors by 5-HT influences the fates of late-developing enteric neurons and new neurons continue to be added to the ENS for at least 3 weeks postnatally in mice. These observations could lead to abnormal development in the second and third trimester. TCAs could influence the development of the ENS through inhibition of the norepinephrine transporter (NET). Expression of the NET seems to be essential for a full

development of enteric neurons and especially for serotonergic neurons. Since the NET is detected early in ontogeny and precedes neuronal differentiation, this suggests that TCAs might influence development of the ENS when exposed early in pregnancy. In summary it might be expected based on this review of the pharmacologic literature [39] that: (i) *in utero* exposure to SSRIs in the first trimester, but also the second and the third trimester will lead to disturbed bowel function and (ii) *in utero* exposure to TCAs in especially the first trimester will lead to disturbed bowel function.

The aim of this cohort study is to explore the use of laxatives and antidiarrhoeal medication as proxy for constipation and diarrhoea respectively, in childhood after SSRI and TCA exposure *in utero*. With this study we intend to demonstrate that medication use in childhood can be used as a proxy for minor birth defects due to medication exposure in pregnancy.

Methods

This study was performed with IADB.nl, which contains pharmacy prescription data of an estimated population of 500 000 individuals from the Netherlands. Registration in the database is irrespective of health insurance and is considered representative for the general population. Each prescription record contains information on the date of dispensing, the quantity dispensed, the dose regimen, the number of days the prescription is valid, the prescribing physician and the Anatomical Therapeutic Chemical code (ATC code). Each patient has a unique anonymous identifier; date of birth and gender are known. Due to the high patient-pharmacy commitment in the Netherlands, the medication records for each patient are virtually complete [40], except for over the counter (OTC) drugs and medication dispensed during hospitalization.

The data for this study were obtained from the 'Pregnancy IADB', which was extracted from the main IADB database. Children were selected by date of birth and the female person (15–50 years) with the same address code was considered to be the mother [41]. Because only the child's birth date is known, the theoretical conception date was determined as the date of birth minus 273 days (i.e. 9 months). The database has been previously described [1, 42].

The data between 1995 and 2009 from the pregnancy database were used. Focusing on our study objective; we determined the relative risk for laxative and antidiarrhoeal medication use in children after *in utero* antidepressant exposure.

Study population, exposure and reference groups

We identified in the period 1995–2009, 35 400 pregnancies occurring to 24 467 women. From these 35 400 pregnan-

cies 36 323 children were born. The exposure to antidepressants was calculated during the three trimesters of pregnancy of each woman. Exposure was defined as the theoretical period of use, from dispensing date until the last day the prescription was valid. Two exposure groups were formed i.e. children of mothers exposed to tricyclic antidepressants (TCAs; ATC code = N06AA) and children of mothers exposed to selective serotonin re-uptake inhibitors (SSRIs; ATC code = N06AB) during pregnancy. In addition we analyzed a group who was exposed to both a SSRI and a TCA (ATC code = N06AA and N06AB). These cases were excluded from the TCA exposed group and SSRI exposed group. All prescriptions of TCAs with less than 0.5 defined daily doses (DDD) per day were excluded, because TCAs are used for treating neuropathic pain in a lower dose than for treating depression.

In the SSRI exposure group we performed sub-analyses for fluoxetine (ATC code = N06AB03) and for paroxetine (ATC code = N06AB05). The time of exposure to antidepressants was divided into the following periods: the whole pregnancy, only the first trimester, only the second and third trimester combined, at least the first trimester and at least the second and third trimester combined.

The reference group consisted of women who did not use any SSRIs or TCAs during pregnancy and during a period of 7 days before pregnancy.

Laxative and antidiarrhoeal medication use (proxy drugs)

The use of laxatives (ATC code = A06) and antidiarrhoeal medication (ATC code = A07C; A07D; A07F; A07X) in the newborn was studied in the exposed groups and the reference group, and was regarded as a proxy for constipation and diarrhoea, respectively. Laxative and anti-diarrhoeal medication use was defined as the starting date of a prescription for these medications.

Analysis

The calculated day of conception was chosen as the starting point to identify in which periods the children were exposed. The day of birth of the children was chosen as the starting point for the follow-up. The incidence rate (IR) of laxative use and of antidiarrhoeal medication use in the defined exposure groups was calculated as the number of incident cases (laxative or antidiarrhoeal users) divided by the time at risk (in years) [43]. The use was studied in the first 5 years of the life of a child. The time at risk was measured from the day of birth until either the first prescription date, the last known date of the child in the database or the end of the study period, whichever occurred first. The exposure groups and reference group were compared and the incidence risk ratio (IRR) and 95% confidence interval (CI) were calculated [43].

Results

Laxatives as proxy for constipation

From the 35 400 pregnancies in our population, 36 323 children were born. Exposure to an SSRI anytime in pregnancy occurred in 512 pregnancies and 527 children. Paroxetine was the most commonly prescribed SSRI ($n = 310$), followed by fluoxetine ($n = 105$), citalopram ($n = 60$), fluvoxamine ($n = 60$), sertraline ($n = 19$) and escitalopram ($n = 2$). Exposure to a TCA anytime in pregnancy occurred in 72 pregnancies and to 76 children. The most commonly used TCA was clomipramine ($n = 40$), followed by amitriptyline ($n = 26$). One woman used three different TCAs during pregnancy. In the period 1995–2009 34 908 children (34 022 pregnancies) were not exposed to any medication.

Table 1 presents the use of laxatives estimated as incidence in the reference group and the different exposure groups (SSRIs, TCA, fluoxetine and paroxetine) as well as the different periods of exposure (anytime, only first trimester, only second and third trimester, at least first trimester and at least second and third trimester). The number of incident cases (antidiarrhoeal medication and laxative users) and the time at risk were used to calculate the IR. SSRI exposure anytime in pregnancy was related to a significant increase in laxative use in the child (IRR = 1.37, 95% IRR 1.11, 1.68). Especially exposure in the second and third trimester seems to be related to an increased use of laxative. At least exposed in the second and third trimester compared with non-exposed is related to an IRR of 1.68 (95% IRR 1.30, 2.18).

In contrast exposure to TCAs shows a significant increase in laxative use of the child when the mother is exposed only in the first trimester (IRR = 1.94, 95% IRR 1.05, 3.62). There was no significant increase seen when exposed to a TCA anytime in pregnancy and the other defined exposure times.

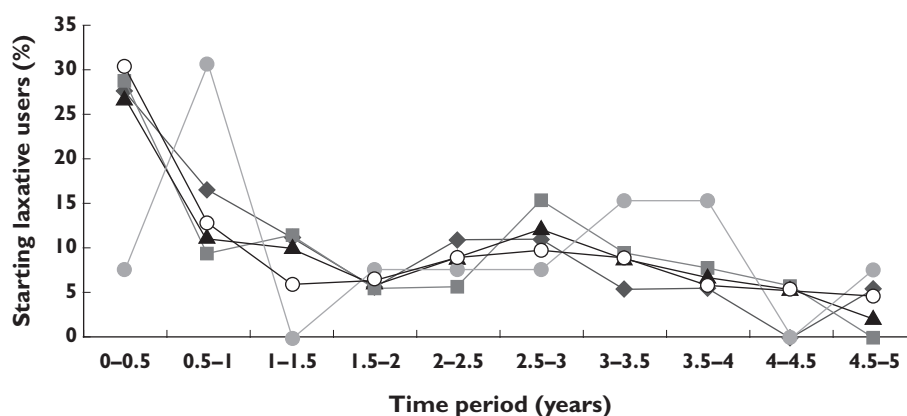
The IRRs of fluoxetine and paroxetine exposure are presented separately. Fluoxetine exposure was related to a higher use of laxatives in the child when exposed only in the second and third trimester (IRR = 2.51, 95% IRR 1.05, 5.05) and borderline significant in the category at least the second and third trimester exposure (IRR = 1.70, 95% IRR 0.99, 2.93). In the paroxetine exposed group a significant increase in laxative use is seen when exposed anytime in pregnancy (IRR = 1.35, 95% IRR 1.03, 1.78), at least in the first trimester (IRR = 1.41, 95% IRR 1.06, 1.88) and at least in the second and third trimester (IRR = 1.72, 95% IRR 1.22, 2.42).

There were 12 pregnancies in which the child was exposed to a TCA and a SSRI in succession. Due to low numbers the IRR was only calculated for exposure anytime in the pregnancy. Exposure to both a TCA and a SSRI compared with non-exposed was related to an IRR of 9.64 (95% IRR 4.82, 19.28).

During the study period 1995–2009 lactulose ($n = 3378$) was the most commonly prescribed laxative, followed by

Table 1The use of laxatives after *in utero* exposure to SSRIs or TCAs

Laxatives Group	Pregnancy period	Children	Laxative users	Time at risk (years)	IR (years)	IRR (95% CI)
Reference						
	Anytime	34 908	4847	119 612	0.0405	1
SSRI exposed						
	Anytime	527	89	1611	0.0552	1.37 (1.11, 1.68)
	Only first trimester	228	31	759	0.0408	1.01 (0.71, 1.68)
	Only second and third trimester	54	10	173	0.0577	1.42 (0.77, 2.65)
	At least first trimester	473	79	1438	0.0549	1.36 (1.09, 1.70)
	At least second and third trimester	299	58	852	0.0681	1.68 (1.30, 2.18)
TCA exposed						
	Anytime	76	13	271	0.0479	1.18 (0.69, 2.04)
	Only first trimester	36	10	127	0.0788	1.94 (1.05, 3.62)
	Only second and third trimester	10	0	—	—	—
	At least first trimester	66	13	229	0.0567	1.40 (0.81, 2.41)
	At least second and third trimester	40	3	144	0.0208	0.51 (0.17, 1.59)
Fluoxetine						
	Anytime	105	18	317	0.0569	1.40 (0.88, 2.23)
	Only first trimester	36	5	128	0.0391	0.96 (0.40, 2.32)
	Only second and third trimester	18	5	49	0.1020	2.51 (1.05, 6.05)
	At least first trimester	87	13	268	0.0486	1.20 (0.70, 2.07)
	At least second and third trimester	69	13	189	0.0689	1.70 (0.99, 2.93)
Paroxetine						
	Anytime	301	52	950	0.0547	1.35 (1.03, 1.78)
	Only first trimester	138	19	477	0.0398	0.98 (0.63, 1.54)
	Only second and third trimester	32	4	111	0.0360	0.89 (0.33, 2.37)
	At least first trimester	269	48	839	0.0572	1.41 (1.06, 1.88)
	At least second and third trimester	163	33	473	0.0698	1.72 (1.22, 2.42)

**Figure 1**

The use of laxatives after *in utero* exposure to SSRIs or TCAs compared with no medicine exposure. The y-axis describes the percentage starting laxatives and the x-axis the time period in which they started using laxatives in years. Fluoxetine (—◆—); Paroxetine (—■—); SSRI (—▲—); TCA (—●—); Reference (—○—)

macrogol ($n = 509$), liquid paraffin ($n = 354$) and bisacodyl ($n = 265$). The pattern of starting laxative use after *in utero* exposure to SSRIs or TCAs is presented in Figure 1. In almost all exposure categories most children started using

laxatives in the first 6 months after birth except for the TCA group where the peak was between 6 months to 1 year and between 2.5–4.5 years after birth. However this could be due to the size of the TCA group.

Table 2
Antidiarrhoeal medication use after *in utero* exposure of SSRIs or TCAs

Antidiarrhoeal medication Group	Pregnancy period	Children	Antidiarrhoeal med users	Time at risk (years)	IR (years)	IRR (95% CI)
Reference						
	Anytime	34 908	1458	12 7471	0.0114	1
SSRI exposed						
	Anytime	527	18	1 747	0.0103	0.90 (0.57, 1.43)
	Only first trimester	228	8	811	0.0099	0.86 (0.43, 1.73)
	Only second and third trimester	54	2	188	0.0107	0.93 (0.23, 3.73)
	At least first trimester	473	16	1 559	0.0103	0.90 (0.55, 1.47)
	At least second and third trimester	299	10	936	0.0107	0.93 (0.50, 1.74)
TCA exposed						
	Anytime	76	9	268	0.0336	2.94 (1.52, 5.66)
	Only first trimester	36	5	135	0.0372	3.26 (1.35, 7.83)
	Only second and third trimester	10	1	37	0.0268	2.35 (0.33, 16.67)
	At least first trimester	66	8	230	0.0347	3.03 (1.51, 6.08)
	At least second and third trimester	40	4	133	0.0300	2.62 (0.98, 6.99)

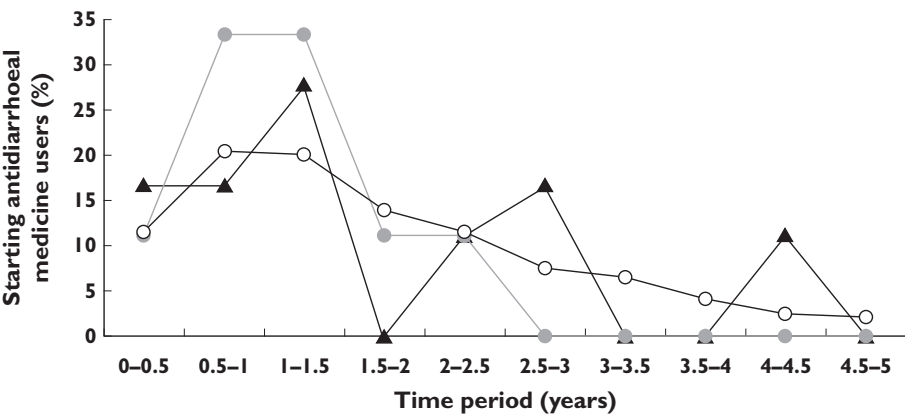


Figure 2
The use of antidiarrhoeal medication after *in utero* exposure of SSRIs or TCAs compared with no medicine exposure. The y-axis describes the percentage of starting laxative and the x-axis the time period in which they start using laxatives in years. SSRI (—▲—); TCA (—●—); Reference (—○—)

Antidiarrhoeal medication as proxy for diarrhoea

In addition to the laxatives, we also studied antidiarrhoeal medication use related to the use of antidepressants by the mother during pregnancy (Table 2). No increase in antidiarrhoeal medication use in the child was seen after exposure to SSRIs *in utero*. In contrast, exposure to TCAs in all pregnancy periods, including the first trimester, seemed to be related to a higher use of antidiarrhoeal medication in the child compared with the not exposed group. In the fluoxetine and paroxetine groups no increase in antidiarrhoeal medication use was seen (data not shown).

During the period 1995–2009 oral rehydration salt formulas ($n = 1330$) were the most commonly used antidiarrhoeal medication, followed by loperamide ($n = 192$).

The time after birth when the children were prescribed an antidiarrhoeal medication was similar for the exposed and the reference groups (Figure 2).

Discussion

This study shows that the use of SSRIs and TCAs in pregnancy increased laxative use in new born children compared with non-exposed children. Children exposed to SSRIs (mainly fluoxetine and paroxetine) in the second and third trimester or to TCAs in the first trimester, more often received laxatives. Combined exposure to TCAs and SSRIs in pregnancy was associated with a 10-fold increase in laxative use. Exposure to SSRIs *in utero* was not associated

with antidiarrhoeal medication use in these children compared with non-exposed children. In contrast, antidiarrhoeal medication use was significantly higher in children exposed to TCAs anytime in pregnancy. So far there is no literature available for comparison with the outcome of this study. In a pharmacologic literature study [39] performed prior to this study we did find indications that exposure to SSRIs and TCAs during pregnancy may be associated with a disturbed development of the ENS.

Selective serotonin re-uptake inhibitors

How can we explain the increased use of laxatives in children exposed to SSRIs during the second and third trimester but not during the first trimester? This might be due to the fact that 5-HT is not only a neurotransmitter but also a growth factor in the primitive ENS that effects the development of late-arising enteric neurons predominantly by activation of the 5-HT_{2B} receptor [44], which could influence the development of the late-arising neurons.

The results with respect to paroxetine showed the same increase in laxative use as SSRIs as a group. However fluoxetine showed a more than two-fold increase when used only in the second and third trimester. Does this indicate that fluoxetine might influence the serotonergic pathways in a different way from paroxetine and the other SSRIs? In the literature review we found that fluoxetine and paroxetine are the only SSRIs that are known to bind to the 5-HT_{2B} receptor, although the selectivity of fluoxetine for this receptor is higher [39]. Since the development of enteric neurons through stimulation of the 5-HT_{2B} receptor persists for a long time and even after birth, a higher selectivity for this receptor might lead to more damage later in pregnancy. This could explain the increased laxative use after fluoxetine exposure during the second and third trimester.

SSRI exposure in all pregnancy periods showed no increase in antidiarrhoeal medication use. SSRIs may not affect the pathways in foetal development that cause diarrhoea. The body may have mechanisms that compensate for the 5-HT concentration changes caused by SSRIs.

Tricyclic antidepressants

Can we also explain the increase in laxative use when exposed exclusively in the first trimester to TCAs? NET is essential for the development of enteric neurons and particularly affects serotonergic neurons [45,46]. Serotonergic neurons develop early in ontogeny [47, 48], which indicates that defects would occur when exposed in early pregnancy. Other arguments that solidify the result that TCAs influence early development of the ENS are that NET is expressed before neuronal differentiation [46] and that expression during sympathetic neuronal development has been linked to acquisition of the noradrenergic phenotype [45].

When exposed to both SSRIs and TCAs in pregnancy the mechanisms of the antidepressants might amplify

each other. This might explain the high increase in laxative use that was seen in our results.

In addition to the increase in laxative use, how do we explain the increase in antidiarrhoeal medication use when exposed to TCAs even though this is not seen when exposed to SSRIs? TCAs also influence noradrenergic pathways and SSRIs do not. It is known that adrenergic receptors are involved in control of intestinal motility: stimulation of intestinal α_1 -, α_2 - and β_2 -adrenoceptors relaxes the smooth muscles in the GI tract, thus slowing down the peristalsis [49, 50] and α_2 -adrenoceptor agonists prevent diarrhoea [51–53]. Due to the TCA induced NE increase, the presynaptic α_2 -adrenoceptor and postsynaptic β - and α_1 -receptor desensitize and down-regulate. Down-regulation of α -adrenoceptors leads to a less efficient adrenergic system which causes increased peristalsis, electrolyte secretion and decreased absorption, which all increase the risk of diarrhoea [51, 52]. Administration of an antagonist can also lead to up regulation of the α_1 -adrenoceptor. Due to the up-regulation the receptors can have a higher response to neurotransmitters. Enhanced expression of the α_{1c} subunit results in smooth muscle hyper-reactivity to acetylcholine (ACh), accelerated colonic transit and increase in defaecation rate [54]. Normal concentrations of NE could have the same effect on up-regulated α_1 -adrenoceptors as an increased concentration of NE in a normal situation. Down- and up-regulation can happen anytime in pregnancy which could be an explanation for the increase in antidiarrhoeal use through affecting the noradrenergic pathways.

Antidepressants compared

Since SSRIs and TCAs both increase laxative use, although through exposure in different trimesters, is it possible that the influence of TCAs on serotonergic pathways causes this increase? 5-HT as a neurotransmitter is involved in the motility of the gut. If serotonergic neurons are lost, normal intestinal motility is diminished (or absent) and transit down the bowel is slowed [55]. Since we have shown that SSRI and TCA exposure influences the development of enteric serotonergic neurons, motility can be diminished in these children. Consequently this leads to slow transit down the bowel and the solution can be laxative use. So it is possible that the serotonergic characteristics of antidepressants cause the increase in laxative use.

Limitations

There are some limitations in using an administrative prescription database because we do not know whether the drugs were actually taken. If the women were not compliant, our results would be an underestimation of the real effect. In addition our method provides no indication of how much of the medication was actually taken or compliance in general. Another limitation is that OTC drugs are

missing. If the children got their laxatives or antidiarrhoeal as OTC drugs this would also lead to an underestimation of the effect.

SSRIs and TCAs are prescribed for treating depression, but also for treating anxiety and personality disorders. Perhaps these diseases themselves can cause constipation or diarrhoea by behavioural changes in the mothers. We have no information about the indication for the prescribed drugs and, therefore, confounding by indication is still possible. Only randomized controlled follow-up studies could prevent this form of confounding. Depression, in general, in The Netherlands is not related to socio-economic status. However, confounding due to socioeconomic factors such as dietary habits leading to constipation or an increased incidence of infective diarrhoea is possible and warrants further investigation.

Oral rehydration salt formulas are the first choice therapy to treat dehydration from diarrhoea, but also from other causes which do not represent disturbed ENS development. The use of laxatives and antidiarrhoeal medication as a proxy for disturbed ENS development may not be an accurate proxy, because they could be used to treat other diseases and this could lead to confounding.

TCAs and SSRIs also bind to receptors that were not investigated (muscarinic M3-receptor, histamine H₁-receptor), but it is unclear what the function of these receptors is in the ontogeny of the ENS. The diversity and numbers of explanations for the results obtained in this study show the complexity of the development of the ENS. More research needs to be done to elucidate fully the role of antidepressants in the development of the ENS.

In conclusion children who were exposed to SSRIs in the second and third trimester or to TCAs in the first trimester more often received laxatives. A 10-fold increase in laxative use was found when exposed to both a SSRI and a TCA during pregnancy. SSRI exposure *in utero* was not associated with antidiarrhoeal medication use in these children, but TCA exposure anytime in pregnancy was. There were no case reports or studies found reporting these associations. The increased laxative use after second and third trimester exposure to SSRIs might be explained through the inhibitory effect of the SERT and because of selectivity for the 5-HT_{2B} receptor which affects the ENS. TCA exposure during the first trimester leads to increased laxative use probably through inhibition of the NET. Exposure of TCAs anytime in pregnancy may lead to increase diarrhoeal use possibly through down-regulation of α_2 -adrenoceptors or up-regulation of the pore forming α_{1c} subunit.

Competing Interests

There are no competing interests to declare.

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